DOI: 10.1002/chem.200701621

Pd-Catalyzed Aryl Amination Mediated by Well Defined, N-Heterocyclic Carbene (NHC)–Pd Precatalysts, PEPPSI**

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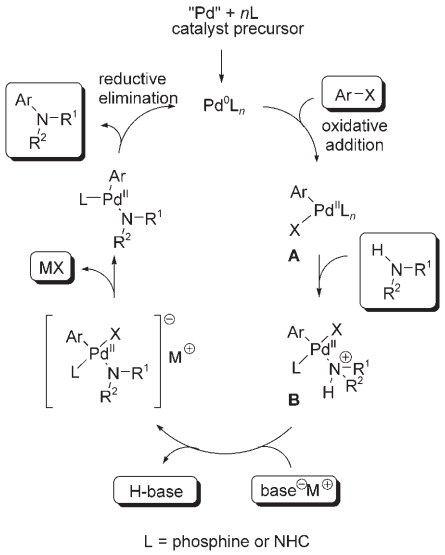
Abstract: Pd–N-heterocyclic carbene (NHC)-catalyzed Buchwald–Hartwig amination protocols mediated by Pd–PEPPSI precatalysts is described. These protocols provide access to a range of hindered and functionalized drug-like aryl amines in high yield with both electron-deficient and electron-rich aryl- and heteroaryl chlorides and bromides. Variations in solvent polarity, base and temperature are tolerated, enhancing the scope and utility of this protocol. A mechanistic rationalization for base strength (pK_b) requirements is also provided.

Keywords: amination · anilines · asymmetric catalysis · carbenes · palladium

Introduction

In 1995, the groups of Buchwald[1] and Hartwig,[2] building on the earlier ground-breaking work of Kosugi,[3] independently reported the first Pd-catalyzed aminations of aryl bromides with free amines.[4] Since these seminal publications, the Buchwald–Hartwig amination reaction has been developed into a valuable synthetic tool.[5] Currently, aryl halides, triflates and tosylates are efficiently coupled with aryl and alkyl amines, amides, sulfonamides, imines, nitrogen-containing heterocycles, and as of very recently, ammonia[6] under a variety of reaction conditions.[5] The proposed catalytic cycle begins with the oxidative addition of a Pd^0 species into the carbon halide or pseudo-halide bond of the aryl halide or pseudo-halide, respectively (Scheme 1). After coordination of the amine, subsequent deprotonation at low temperatures results in an anionic amido complex, whereas at higher temperatures the neutral tricoordinated species is preferred. Finally, reductive elimination yields the product concomitant with the regeneration of Pd^0.[5,7]



Scheme 1. Proposed mechanism for Pd-catalyzed amination at low temperature. A palladium-amide species is formed in the presence of a strong base (i.e., *t*BuOK).

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[**] PEPPSI: pyridine, enhanced, precatalyst, preparation, stabilization, and initiation

The most commonly used ligands for this transformation are bulky tertiary phosphines.[5] In recent years, substantial progress has been achieved in optimizing the phosphine ligands′ structure to achieve high yields with a diverse array of substrates (Figure 1).[8–15] Presently, Buchwald's biaryl

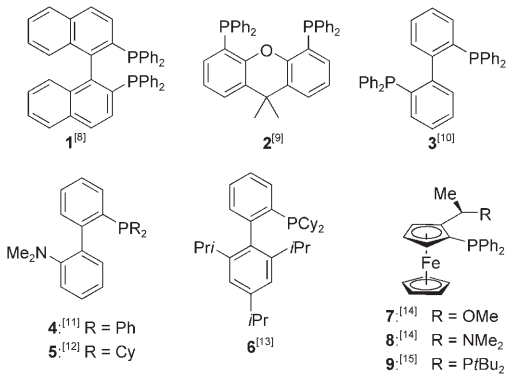


Figure 1. Highly-active phosphine ligands in Pd-catalyzed amination reactions.

phosphine **6** is shown to have the broadest applicability in Pd-catalyzed amination.[13] Recently, the use of *N*-heterocyclic carbenes (NHCs) as ligands in Pd-catalyzed aminations have shown much promise.[16] Most early NHC-based protocols for Buchwald–Hartwig amination relied on generation of the free carbene in situ from a precursor azolium salt in the presence of a Pd^{II} or Pd^{0} source.[17] However, the rate and efficiency of active catalyst formation is difficult to control under these conditions. This not only carries the potential of wasting precious Pd and ligand precursor, but also results in poor reproducibility. This uncertainty surrounding the stoichiometry and composition of the active species is a major impediment to drawing mechanistic interpretation from the results, retarding both the understanding and further development of these processes.[18] Collectively, the aforementioned factors have slowed widespread adoption of NHC-based methodology. For these reasons, we[19] and others[16c,20] have developed well-defined NHC–palladium precatalysts. Our own studies led to the preparation of easily synthesized precatalysts, the PEPPSI series[19] (Figure 2, **10**–**13**), which have shown excellent activity and substrate tolerance in Suzuki–Miyaura,[19] Negishi[21] and Kumada–Tamao–Corriu[22] reactions. In an ongoing effort to enhance the scope and utility of Pd–PEPPSI complexes, we herein report on our findings on the use of these complexes in Pd-catalyzed amination.

Results and Discussion

From the outset our aim was to develop an effective and user-friendly, easily implemented process requiring only general laboratory technique to carry out the amination protocol. Additionally, the process should be scalable and able to

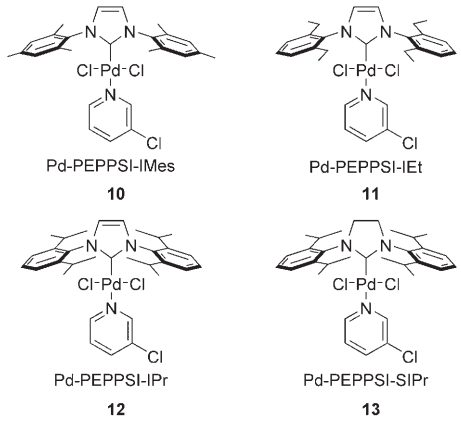
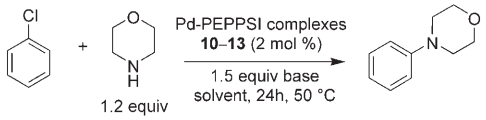


Figure 2. Pd-PEPPSI (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation) precatalyst complexes.

withstand a broad range of functionalized substrates for use in industrial and academic laboratories alike. The choice of base has often been found to be critical. The most successful and widely utilized bases are sodium and potassium *tert*-butoxide, though weaker bases (e.g., Cs_2CO_3)[23] have also been employed. As a start we investigated the stronger base potassium *tert*-butoxide (Table 1). We found that complexes **12**

Table 1. Optimization of reaction conditions for Pd-catalyzed amination.



Entry	Complex	Solvent	Base	Conversion [%][a]
1	**12**	DMSO	*t*BuOK	65
2	**12**	DMI	*t*BuOK	100
3	**12**	DMF	*t*BuOK	100
4	**12**	*t*BuOH	*t*BuOK	75
5	**12**	MeOH	*t*BuOK	0
6	**12**	DME	*t*BuOK	98
7	**12**	THF	*t*BuOK	90
8	**12**	1,4-dioxane	*t*BuOK	100
9	**12**	toluene	*t*BuOK	100
10	**10**	DME	*t*BuOK	8
11	**11**	DME	*t*BuOK	7
12	**12**	DME	*t*BuOK	93
13	**13**	DME	*t*BuOK	91
14	**12**	DME	*t*BuOK	99[b]
15	**13**	DME	*t*BuOK	100[b]
16	**12**	DME	*t*BuOK	61[c]
17	**12**	DME	Cs_2CO_3	39[d]

[a] Percent conversion was assessed by GC/MS analysis using undecane as a calibrated internal standard; reactions were performed in duplicate and the average yield is reported. Control experiment omitting **12** resulted in 0% conversion. [b] Reaction was conducted at RT. [c] After 15 s at RT. [d] Reaction was conducted at 70 °C.

and **13** functioned as excellent catalysts, achieving high yields in a variety of solvents ranging from non-polar toluene to significantly more polar DMF, DMI and *t*BuOH (entries 9, 2–4). Interestingly, the use of methanol (entry 5) re-

sulted in no detectable product formation with a substantial amount of palladium black being formed during the course of the reaction. The reasons for this remain unclear as *t*BuOH was well tolerated, however, the absence of β-hydrogen atoms may be important. As expected,[22,24] we found the reaction yield to be highly dependant on the steric environment surrounding the palladium center, with more sterically encumbered Pd–PEPPSI complexes **12** and **13** providing higher yields relative to **10** and **11** (entries 10–13). Impressively, after just 15 seconds a 61% conversion was realized with complex **12** (entry 16). Reactions carried out at room temperature were equally effective (entries 14 and 15). These results, in addition to earlier reports,[7] suggest that for effective amination a sterically demanding yet flexible environment in the vicinity of the metal center is essential.

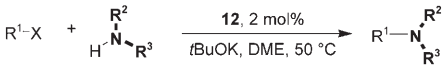
Using the optimized conditions allowed for the coupling of a variety of aryl- and heteroaryl halides with a selection of amines in high yield utilizing only standard laboratory techniques (Table 2). Notably, sterically-encumbered aryl chlorides (products **17** and **18**) or amines (**19** and **21**), and heteroaromatic halides (**20**, **22**, and **24**) all proceeded in high yields. In addition, compound **24** was prepared on a 26-gram scale to demonstrate protocol scalability.

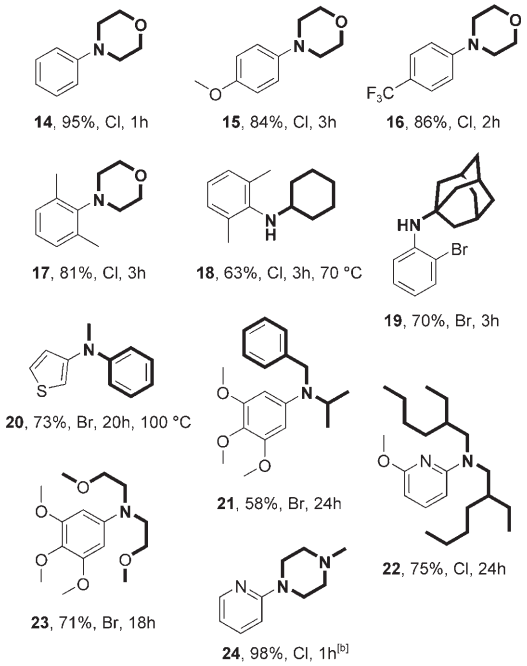
Following these results, we investigated room temperature amination (Table 3). We were pleased to find that both hindered substrates (leading to **26**, **30** and **33**) as well as a variety of heterocycles (leading to **14**–**17**, **27**–**29**, **31** and **32**) were compatible with this room temperature protocol. The reaction between the highly sterically-hindered substrates 2,6-diisopropylaniline and 2-chloro-*m*-xylene, affording **30** in 90% yield, is noteworthy.

We then turned our attention to carbonates as a milder, less expensive and more functional group and air/moisture-tolerant alternative to alkoxide bases. Based on our encouraging preliminary results (Table 1, entry 17), we decided to further evaluate Cs_2CO_3 base (Table 4). Although alcohol-based solvents were ineffective (entries 9 and 10) the employment of ethereal solvents resulted in high yields (entries 2, 3 and 6). The use of polar aprotic solvents DMSO and CH_3CN (entries 7 and 8) was ineffective, however, amide-based solvents such as DMI were effective (entry 4).

As we expanded our substrate study, it became apparent that the process was not as effective with less nucleophilic amines or more electron-rich aryl halides. For example, the coupling of *p*-bromoanisole with morpholine provided 27% yield of isolated product and *N*-methylaniline with *p*-chlorobenzotrifluoride provided 21%. Compared to the weaker, heterogenous Cs_2CO_3, the increased basicity of alkali *tert*-butoxide (a homogeneous base) leads to improved yields (Tables 1 and 4). The interpretation of these results is not straightforward. Buchwald–Hartwig amination entails a

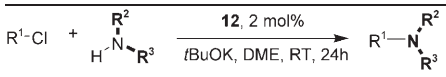
Table 2. Pd-catalyzed amination substrate study.[a]

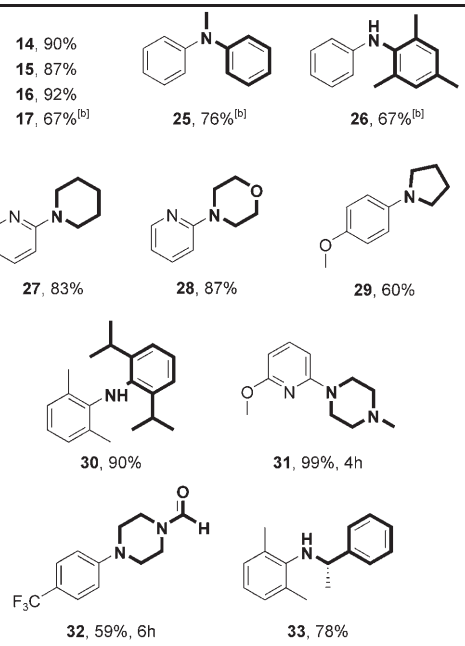




[a] Reactions were performed on a 1 mmol scale (aryl halide) with 1.2 mmol amine, 1.5 mmol *t*BuOK and 20 μmol **12** in 1 mL 1,2-dimethoxyethane (DME) at 50 °C unless indicated otherwise. [b] Reaction was performed on a 150 mmol scale (2-chloropyridine) with 180 mmol amine, 225 mmol *t*BuOK and 3 mmol **12** in 150 mL DME.

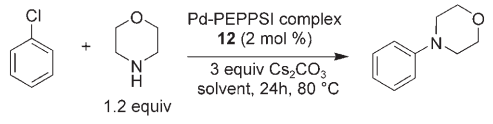
Table 3. Pd-catalyzed aminations at room temperature.[a]





[a] Reactions were performed on a 1 mmol scale (aryl halide) with 1.2 mmol amine, 1.5 mmol *t*BuOK and 20 μmol **12** in 1 mL 1,2-dimethoxyethane (DME) at room temperature for 24 h. [b] Reaction was performed using **13** in place of **12**.

Table 4. Optimization of reactions conditions using Cs_2CO_3 as base.



Entry	Solvent	Conversion (isolated yield, %)[a]
1	DMF	60
2	1,4-dioxane	57
3	DME	82 (89)
4	DMI	72
5	toluene	48
6	THF	87 (72)
7	DMSO	0
8	CH_3CN	0
9	*i*PrOH	0
10	MeOH	0

[a] Percent conversion was assessed by GC/MS analysis using undecane as a calibrated internal standard; reactions were performed in duplicate and the average conversion is reported. Control experiment omitting **12** resulted in 0% conversion.

larger number of possible mechanistic pathways than C–C bond forming reactions. For example, Hartwig has shown that the presence of nucleophilic alkoxides[25] and amines, which form complexes with various intermediates of the catalytic cycle (Scheme 1), leads to alternative catalytic cycle pathways. The nature of the spectator ligand (NHC vs phosphine) additionally complicates the picture. Even though NHCs are often billed as "phosphine mimics", there are significant differences in the electronic properties and the steric topology of the active catalyst between each ligand class. Therefore, the assumption that both types of ligands would share identical mechanisms and rate-determining step might not be justified. For example, a recent computational study of the Heck–Mizoroki reaction revealed that for Pd–NHC catalysts, a cationic pathway is preferred and olefin insertion is the rate-determining step. Conversely, for Pd–phosphine catalysts a neutral pathway is preferred and oxidative addition is the rate-determining step. In our study, the difference of yields observed upon change of base points to the deprotonation of the Pd-bound amine being the most likely rate-determining step of the process. Compared to the extensive mechanistic and computational studies[25,26] with phosphine ligands conducted by the groups of Buchwald and Hartwig, there is a single DFT computational paper on the Buchwald–Hartwig arylation with carbene ligands.[27] Significantly, this work does not include calculations of the crucial deprotonation of the Pd-bound amine step. However, it could be inferred from studies of other cross-coupling reactions that the strongly σ-donating NHC ligand would render the oxidative addition facile, and the steric bulk of the IPr ligand would enhance the rate of reductive elimination. The much lower yields obtained with Pd–PEPPSI complexes of the less sterically encumbered carbenes (**10** and **11**, Figure 2 and Table 1) corroborate this notion. The low acidity of amines ($pK_a \approx 35$) requires that deprotonation is facilitated by complexation of the amine to the oxidative addition intermediate **A** (Scheme 1) acting as a Lewis acid. A relatively electron-poor palladium center should promote a correspondingly high degree of amine coordination (**B**, Scheme 1). This will serve to lower the pK_a of the amine proton, which is particularly important for the comparatively weak carbonate bases.[25b,28] It must also be taken into account that this step is very sensitive to the steric bulk of the amine.[26a] After the aryl halide undergoes oxidative addition, the aryl moiety becomes a ligand on palladium and therefore offers the intriguing possibility to conduct a Hammett analysis of this reaction (Figure 3).

If the argument of Pd^{II}-assisted amine deprotonation as the rate-determining step holds, the amination yields should increase as the aryl halide becomes more electron deficient provided such substitution does not also increase the rate of catalyst death. We compared the initial reaction rates (Figure 3, top) and yields (Figure 3, bottom) of Buchwald–Hartwig amination of a series of aryl bromides and chlorides with morpholine (Figure 3, reaction 1) and found this to be the case. To rule out the possibility that these results are due to increased rate of oxidative addition, we subjected the same halide partners to the Suzuki–Miyaura reaction (Figure 3, reaction 2) and found that all aryl chlorides gave essentially the same level of reaction. Moreover, the yields of Buchwald–Hartwig amination were identical for aryl bromides and chlorides carrying the same *p*-substituent within experimental error. Taken together, these results are consistent with the notion that oxidative addition is not the rate-determining step with IPr NHC ligand. Therefore, we predicted that Cs_2CO_3 could be employed as a base only when the substitution pattern of the aryl halide and the amine partner promote efficient deprotonation of the intermediate **B** (Scheme 1) or the transition state preceding it; 1) the amine must be sufficiently nucleophilic to form **B** (Scheme 1) and/or 2) the organo halide must be sufficiently electron-deficient. It has been demonstrated that such pairing can also increase the rate of reductive elimination for phosphine–Pd catalysts.[29]

Armed with this rationale, we then evaluated the Cs_2CO_3 conditions with a variety of heterocycle-containing coupling partners that fulfilled the above criteria. We found that a wide range of couplings could be promoted by Cs_2CO_3 as the base (Table 5). Substituted quinoline (**34** and **41**), pyridine (**36** and **43**), pyrazine (**35**, **37**–**39**, **42**, **44** and **45**) pyridazine (**46** and **47**) and tetrazole (**40**) derivatives were coupled with a variety of substituted amines in good to excellent yields. Interestingly, only upon slow addition of 3-halopyridines and 5-halopyrimidines to the reaction mixture at 80 °C were optimal yields obtained (Table 6, entries **48**–**55**). In this case, the slightly more flexible SIPr ligand was necessary. It is possible that the specific electronic nature of these particular N-heterocycles could act as catalytic poisons and presumably lead to a decrease in the turnover frequency of the catalyst. At high temperature, β-hydride elimination leading to reduction of the aryl bromide also becomes a concern. The slow addition of the aryl halide would minimize the effect of these side reactions.

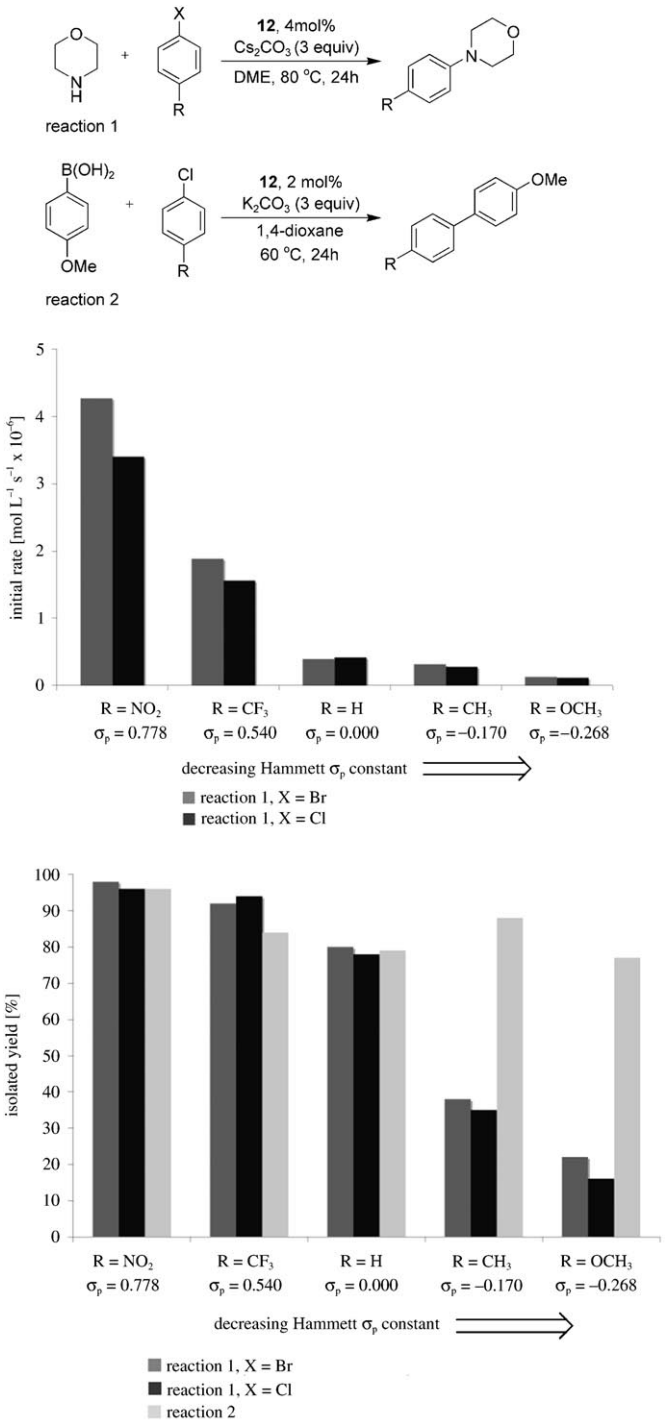
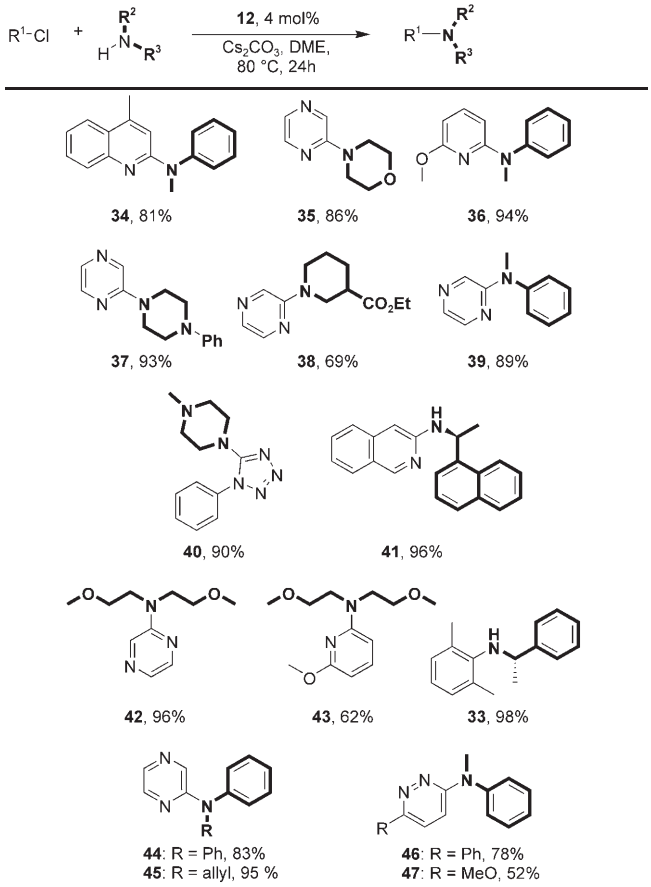


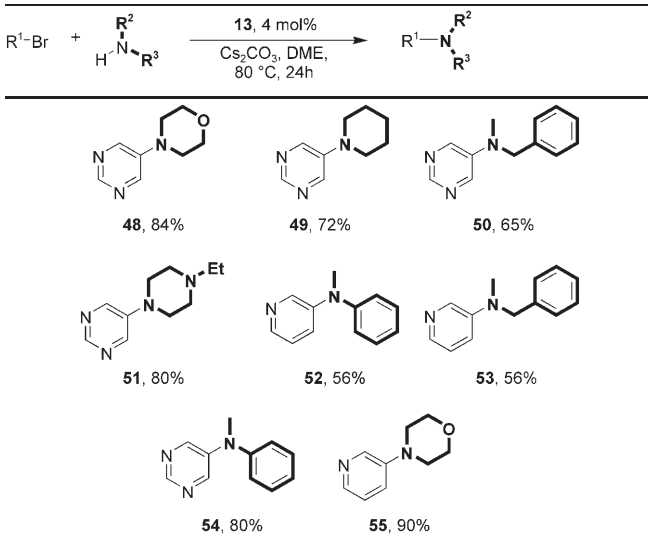
Figure 3. Top: Effect of *p*-substituted aryl halides (varying Hammett sigma constants (σ_p)) on initial reaction rates for Pd–PEPPSI-IPr (**12**)-catalyzed amination (reaction 1). Reaction rates were calculated from the linear portion ($t = 0$ to 240 min) of a product concentration versus time plot. Reactions were performed on a 2 mmol scale (aryl halide) with 3 mmol morpholine, 3 mmol Cs_2CO_3 and 4 mol% **12** in 2 mL 1,2-dimethoxyethane (DME) at 80°C. Products were quantified by GC/MS analysis using undecane (100 μL mmol^{-1} of aryl halide) as a calibrated internal standard. Bottom: Effect of *p*-substituted aryl halides (varying Hammett sigma constants (σ_p)) on isolated yields (24 h) for Pd–PEPPSI-IPr (**12**)-catalyzed amination (reaction 1) and Suzuki–Miyaura reaction (reaction 2). Reactions were performed in duplicate and the average isolated yield is reported.

Table 5. Substrate study using Cs_2CO_3 base.[a]



[a] Reactions performed on a 1 mmol scale (aryl halide) with 1.2 mmol amine, 3.0 mmol Cs_2CO_3 and 40 μmol **12** in 1 mL 1,2-dimethoxyethane (DME) at 80°C for 24 h.

Table 6. Pd-catalyzed amination of 3-halopyridines and 5-halopyrimidines.[a]



[a] Reactions performed on a 1 mmol scale (aryl halide) with 1.2 mmol amine, 3.0 mmol Cs_2CO_3 and 40 μmol **12** in 1.5 mL 1,2-dimethoxyethane (DME) at 80°C for 24 h. The aryl halide was added dropwise as a solution in DME (1 mL) over 30 min. Refer to the Experimental Section for complete details.

Conclusion

In conclusion, we have developed practical, Pd-catalyzed Buchwald–Hartwig amination protocols utilizing Pd–PEPPSI precatalysts **12** and **13**. These protocols allow the preparation of a range of structurally intriguing, drug-like aromatic amines. Both electron-deficient and electron-rich aryl- and heteroaryl halides show good to excellent conversions; sterically encumbered reacting partners were also well tolerated. Pd–PEPPSI-IPr (**12**) was also found to accept significant changes in solvent polarity, which would allow for optimization of reaction conditions on a case-by-case basis if particular reactant pairings behave uniquely. Furthermore, studies carried out indicate that it is possible to utilize Cs_2CO_3 in place of more commonly used KO*t*Bu, permitting the use of base sensitive substrates.

Experimental Section

General experimental methods: All reagents were purchased from commercial sources and were used without further purification, unless indicated otherwise. Dry 1-methyl-2-pyrrolidinone (NMP), 1,2-dimethoxyethane (DME), and 1,3-dimethyl-2-imidazolidinone (DMI) were purchased from Fluka, stored over 4 Å molecular sieves, and handled under Argon. Anhydrous methanol, *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were purchased from Sigma-Aldrich Inc. and handled under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Toluene was distilled from calcium hydride prior to use. All reaction vials (screw-cap threaded, caps attached, 17×60 mm) were purchased from Fischer Scientific. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Thin layer chromatography (TLC) was performed on Whattman 60 F_{254} glass plates and were visualized using UV light (254 nm), potassium permanganate or phosphomolybdic acid stains. Column chromatography purifications were carried out using the flash technique on Silicycle silica gel 60 (230–400 mesh). NMR spectra were recorded on a Bruker 400 AV spectrometer or a Bruker 300 AV spectrometer, as indicated. The chemical shifts (δ) for ^{1}H are given in ppm referenced to the residual proton signal of the deuterated solvent. The chemical shifts (δ) for ^{13}C are referenced relative to the signal from the carbon of the deuterated solvent. ^{13}C APT spectra represent a positive set of peaks (indicated by (+)) for quaternary carbons as well as carbon atoms with even number of protons and a negative set of peaks (indicated by (−)) for carbon atoms with odd number of protons. Gas chromatography was performed on Varian Series GC/MS/MS 4000 System.

General Procedure A: **Pd-Catalyzed amination utilizing KO*t*Bu** (Tables 2 and 3): In air, potassium *tert*-butoxide (1.5 mmol, 169 mg) and Pd–PEPPSI-IPr (**12**, 2 mol%, 13.6 mg) or Pd–PEPPSI-SIPr (**13**, 2 mol%, 13.6 mg) were weighed into a 3 mL screw-cap threaded vial that was sealed with a septum and purged with argon (3×). The amine (1.2 mmol) was added via syringe, and the reaction was allowed to stir for 2–3 minutes. DME (1 mL) was then injected via syringe followed by the aryl halide (1.0 mmol). If the aryl halide was a solid, it was introduced into the vial prior to purging with argon. At this time, the reaction stirred for 24 h at the indicated temperature, unless specified otherwise. The reaction mixture was filtered through a bed of Celite and washed with Et_2O. The filtrate was concentrated in vacuo and purified via silica gel flash chromatography. Pd–PEPPSI-IPr: [(1,3-(2,6-Diisopropylphenyl)imidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride]; Pd–PEPPSI-SIPr: (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) (3-chloropyridyl) palladium(II) dichloride.

General Procedure B: **Pd-Catalyzed amination utilizing Cs_2CO_3** (Table 5 and Figure 3): In air, cesium carbonate (3.0 mmol, 980 mg) and Pd–PEPPSI-IPr (**12**, 4 mol%, 27 mg) were weighed into a 3 mL screw-cap threaded vial that was sealed with a septum and purged with argon (3×). The aryl halide (1.0 mmol), the amine (1.5 mmol) and DME (1 mL) were subsequently added via syringe. If the aryl halide was a solid, it was introduced into the vial prior to purging with argon. The reaction was stirred for 24 h at 80 °C, unless specified otherwise. At this time, the reaction mixture was filtered through a bed of Celite and washed with Et_2O. The filtrate was concentrated in vacuo and purified via silica gel flash chromatography.

General Procedure C: **Pd-Catalyzed amination of 3-halopyridines and 5-halopyrimidines utilizing Cs_2CO_3** (Table 6): In air, Cs_2CO_3 (3.0 mmol, 980 mg) and Pd–PEPPSI-IPr (**12**, 4 mol%, 27 mg) or Pd–PEPPSI-SIPr (**13**, 4 mol%, 27 mg) were weighed into a 3 mL screw-cap threaded vial that was sealed with a septum and purged with argon (3×). The amine (2.1 mmol) and dry DME (0.5 mL) were added sequentially. The reaction mixture was stirred at 80 °C until a green-yellow color persisted (indicative of catalyst activation; length of stirring time varies with amine, typically ranging anywhere from 5–60 min). The aryl halide (1.0 mmol) was then added as a solution in dry DME (1 mL) drop wise over 30 min. The reaction was then stirred for 24 h at 80 °C. At this time, the reaction mixture was filtered through a bed of Celite and washed with Et_2O. The filtrate was concentrated in vacuo and purified via silica gel flash chromatography.

***N*-(Phenyl)morpholine (14)** (Tables 2 and 3 and Figure 3): Following general procedure A (50 °C), 155 mg of **14** (95% yield) were isolated (R_f = 0.35, 10% Et_2O in pentane) as a white crystalline solid (m.p. 52–53 °C; lit. m.p. 54–55 °C).[30] Following general procedure A (RT), 147 mg of **14** (90%) were isolated. Following procedure B, 129 mg of **14** (79% yield) were isolated. The spectral data were in accordance with those reported in the literature.[31]

***N*-(4-Methoxyphenyl)morpholine (15)** (Tables 2 and 3 and Figure 3): Following general procedure A (50 °C), 162 mg of **15** (84% yield) were isolated (R_f = 0.2, step gradient, 10% Et_2O in pentane followed by 25% Et_2O in pentane) as a white crystalline solid (m.p. 67–68 °C; lit. m.p. 71–72 °C).[32] Following general procedure A (RT), 168 mg of **15** (87%) were isolated. Following general procedure B, 52 mg (27% yield, X = Cl) and 31 mg (16%, X = Br) of **15** were isolated. The spectral data were in accordance with those reported in the literature.[33]

***N*-(4-Trifluoromethylphenyl)morpholine (16)** (Tables 2 and 3 and Figure 3): Following general procedure A (50 °C), 200 mg of **16** (86% yield) were isolated (R_f = 0.3, 10% Et_2O in pentane) as a white crystalline solid (m.p. 57–58 °C; lit. m.p. 58 °C).[34] Following general procedure A (RT), 213 mg of **16** (92%) were isolated. Following general procedure B, 213 mg of **16** (92% yield) were isolated. The spectral data were in accordance with those reported in the literature.[31]

***N*-(2,6-Dimethylphenyl)morpholine (17)** (Tables 2 and 3): Following general procedure A (50 °C), 155 mg of **17** (81% yield) were isolated (R_f = 0.3, 5% Et_2O in pentane) as a white crystalline solid (m.p. 83–84 °C; lit. m.p. 86 °C).[32] Following general procedure A (RT), 128 mg of **17** (67%) were isolated. The spectral data were in accordance with those reported in the literature.[35]

***N*-Cyclohexyl-2,6-dimethylaniline (18)** (Table 2): Following general procedure A (50 °C), 128 mg of **18** (63% yield) were isolated (R_f = 0.4, 5% Et_2O in pentane) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 7.6 Hz, 2H), 6.80 (t, J = 7.6 Hz, 1H), 3.00–2.90 (m, 2H), 2.29 (s, 6H), 2.05–1.95 (m, 2H), 1.82–1.72 (m, 2H), 1.70–1.60 (m, 1H), 1.32–1.10 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2 (+), 129.0 (+), 128.8 (−), 121.1 (−), 56.2 (−), 35.1 (+), 26.0 (+), 25.7 (+), 19.1 ppm (−); elemental analysis calcd (%) for $C_{14}H_{21}N$: C 82.70, H 10.41, N 6.89; found: C 82.50, H 10.12, N 7.01.

***N*-Phenyl-1-adamantylamine (19)** (Table 2): Following general procedure A (50 °C), 214 mg of **19** (70% yield) were isolated (R_f = 0.2, step gradient, 5% Et_2O in pentane followed by 25% Et_2O in pentane) as a beige crystalline solid (m.p. 109–111 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 7.2 Hz, 1H), 4.22 (s, 1H), 2.34 (s, 3H), 2.01 (s, 6H), 1.80–1.68 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) APT: δ 143.6 (+), 132.7 (−), 127.7 (−), 118.3 (−), 116.7 (−), 112.9 (+), 52.6 (+), 43.2 (+), 36.5 (+),

29.7 ppm (−); elemental analysis calcd (%) for $C_{16}H_{20}NBr$: C 62.75, H 6.58, N 4.57; found: C 62.61, H 6.79, N 4.65.

***N*-Methyl-*N*-phenyl-3-aminothiophene (20)** (Table 2): Following general procedure A (1 mL of toluene at 100 °C instead of DME at 80 °C), 138 mg of **20** (73 % yield) were isolated (R_f = 0.2, step gradient, 5 % Et_2O in pentane followed by 25 % Et_2O in pentane) as a yellow oil. The spectral data were in accordance with those reported in literature.[36]

***N*-Benzyl-*N*-isopropyl-3,4,5-trimethoxyaniline (21)** (Table 2): Following general procedure A (50 °C), 176 mg of **21** (58 % yield) were isolated (R_f = 0.30, 20 % Et_2O in pentane) as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5H), 5.98 (s, 2H), 4.40 (s, 2H), 4.22 (quin., J = 6.4 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 6H), 1.27 ppm (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) APT: δ = 153.6 (+), 146.2 (+), 140.9 (+), 129.8 (+), 128.5 (−), 126.5 (−), 126.3 (−), 92.0 (−), 61.0 (−), 55.9 (−), 49.0 (−), 48.9 (+), 20.0 ppm (−); elemental analysis calcd (%) for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found: C 72.01, H 8.24, N 4.66.

***N*,*N*-Bis(2-ethylhexyl)-6-methoxy-2-aminopyridine (22)** (Table 2): Following general procedure A (50 °C), 261 mg of **22** (75 % yield) were isolated (R_f = 0.25, pentane) as a light yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, J = 8.0 Hz, 1H), 5.97 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.42–3.32 (m, 4H), 1.90–1.78 (m, 2H), 1.48–1.21 (m, 16H), 0.95–0.85 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ = 162.9 (+), 157.3 (+), 139.3 (−), 97.2 (−), 95.0 (−), 53.5 (+), 52.8 (−), 37.4 (−), 30.7 (+), 28.8 (+), 24.0 (+), 23.2 (+), 14.1 (−), 10.8 ppm (−); elemental analysis calcd (%) for $C_{22}H_{40}N_2O$: C 75.81, H 11.57, N 8.04; found: C 75.71, H 11.84, N 8.47.

3,4,5-Trimethoxy-*N*,*N*-bis(2-methoxyethyl)aniline (23) (Table 2): Following general procedure A (50 °C), the crude residue was taken up in Et_2O (100 mL) and washed with 1 M HCl (3 × 50 mL). The organic layer was discarded and the combined aqueous layers were adjusted to pH ≈10 using a solution of 10 M KOH. The aqueous layer was extracted with Et_2O (3 × 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Following this, 213 mg of **23** (71 % yield) were isolated (R_f = 0.60, step gradient, 60 % Et_2O in pentane followed by 80 % Et_2O in pentane) as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 2H), 3.85 (s, 6H), 3.78 (s, 3H), 3.60–3.48 (m, 8H), 3.38 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) APT: δ = 153.8 (+), 145.0 (+), 129.8 (+), 90.6 (−), 70.5 (+), 61.1 (−), 59.0 (−), 56.1 (−), 51.5 ppm (+); elemental analysis calcd (%) for $C_{15}H_{25}NO_5$: C 60.18, H 8.42, N 4.68; found: C 59.92, H 8.60, N 4.97.

1-Methyl-4-(pyridin-2-yl)piperazine (24) (Table 2): Following general procedure A (50 °C, completed using 150 mmol of aryl chloride), the crude material was taken up in Et_2O (1 L) and washed with 1 M HCl (2 × 500 mL). The organic layer was discarded and the combined aqueous layers were adjusted to pH ≈10 using a solution of 10 M KOH. The aqueous layer was extracted with Et_2O (3 × 500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Following this, 26.1 g of **24** (98 % yield) were isolated as a light yellow, viscous oil. The spectral data were in accordance with those reported in literature.[37]

***N*-Methyldiphenylamine (25)** (Table 3): Following general procedure A (RT), 139 mg of **25** (76 % yield) were isolated (R_f = 0.3, 5 % Et_2O in pentane) as a white, crystalline solid. The spectral data were in accordance with those reported in literature.[33]

2,4,6-Trimethyl-*N*-phenylaniline (26) (Table 3): Following general procedure A (RT), 141 mg of **26** (67 % yield) were isolated (R_f = 0.3, 5 % Et_2O in pentane) as a colorless oil.[33]

2-Piperidinylpyridine (27) (Table 3): Following general procedure A (RT), 135 mg of **27** (83 % yield) were isolated (R_f = 0.3, 10 % Et_2O in pentane) as a colorless oil. The spectral data were in accordance with those reported in literature.[20g]

4-(Pyridin-2-yl)morpholine (28) (Table 3): Following general procedure A (RT), 142 mg of **28** (87 % yield) were isolated (R_f = 0.35, 50 % Et_2O in pentane) as a yellow oil. The spectral data were in accordance with those reported in literature.[20f]

1-(4-Methoxyphenyl)pyrrolidine (29) (Table 3): Following general procedure A (RT), 107 mg of **29** (60 % yield) were isolated (R_f = 0.4, 10 % Et_2O in pentane) as a light yellow oil. The spectral data were in accordance with those reported in literature.[38]

***N*-(2,6-Dimethylphenyl)2,6-diisopropylaniline (30)** (Table 3): Following general procedure A (RT), 253 mg of **30** (90 % yield) were isolated (R_f = 0.3, 5 % Et_2O in pentane) as a colorless oil. The spectral data were in accordance with those reported in literature.[33]

1-(6-Methoxypyridin-2-yl)-4-methylpiperazine (31) (Table 3): Following general procedure A (RT), the crude residue was taken up in Et_2O (100 mL) and washed with 1 M HCl (2 × 50 mL). The organic layer was discarded and the combined aqueous layers were adjusted to pH ≈10 using a solution of 10 M KOH. The aqueous layer was extracted with Et_2O (3 × 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Following this, 205 mg of **31** (99 % yield) were isolated (R_f = 0.50, 10 % methanol in dichloromethane) as a light yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (t, J = 8.1 Hz, 1H), 6.15 (d, J = 7.8 Hz, 1H), 6.08 (d, J = 8.1 Hz, 1H), 3.87 (s, 3H), 3.54 (t, J = 5.1 Hz, 4H), 2.51 (t, J = 5.1 Hz, 4H), 2.34 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 163.1 (+), 158.3 (+), 140.1 (−), 98.2 (−), 98.1 (−), 54.9 (+), 52.9 (−), 46.2 (−), 45.2 ppm (+); elemental analysis calcd (%) for $C_{11}H_{17}N_3O$: C 63.74, H 8.27, N 20.27; found: C 63.42, H 8.42, N 20.67.

1-Formyl-4-(4-(trifluoromethyl)phenyl)piperazine (32) (Table 3): Following general procedure A (RT), 153 mg of **32** (59 % yield) were isolated (R_f = 0.25, ethyl acetate) as a white solid (m.p. 70–73 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.74 (t, J = 4.8 Hz, 2H), 3.57 (t, J = 4.8 Hz, 2H), 3.32 (t, J = 5.2 Hz, 2H), 3.28 ppm (t, J = 5.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ = 160.7 (−), 153.0 (+), 126.5 ((−), q, J = 3.8 Hz), 124.6 ((+), q, J = 269 Hz), 121.5 ((+), q, J = 33 Hz), 115.3 (−), 49.2 (+), 48.0 (+), 45.1 ppm (+), 39.6 ppm (+); elemental analysis calcd (%) for $C_{12}H_{13}F_3N_2O$: C 55.81, H 5.07, N 10.85; found: C 56.14, H 5.36, N 10.77.

(*S*)-2,6-Dimethyl-*N*-(1-phenylethyl)aniline (33) (Table 3): Following general procedure A (RT), 176 mg of **33** (78 % yield) were isolated (R_f = 0.4; 5 % Et_2O in pentane) as a yellow, viscous oil. Following general procedure B, 221 mg of **33** (98 %) were isolated. $[\alpha]_D^{20}$ = −100.8° (c = 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.25 (m, 5H), 7.05 (d, J = 7.5 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 4.41 (q, J = 6.8 Hz, 1H), 3.24 (br. s, 1H), 2.26 (s, 6H), 1.60 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.4 (+), 145.0 (+), 130.5 (+), 128.9 (−), 128.5 (−), 127.0 (−), 126.2 (−), 121.7 (−), 56.8 (−), 22.7 (−), 19.0 ppm (−); elemental analysis calcd (%) for $C_{16}H_{19}N$: C 85.28, H 8.50, N 6.22; found: C 84.97, H 8.26, N 5.90.

***N*,4-Dimethyl-*N*-phenylquinolin-2-amine (34)** (Table 5): Following general procedure B, 201 mg of **34** (81 % yield) were isolated (R_f = 0.15, 3 % Et_2O in pentane) as colorless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.75 (m, 2H), 7.60 (dt, J = 7.5, 1.5 Hz, 1H), 7.50–7.40 (m, 2H), 7.38–7.25 (m, 4H), 6.64 (s, 1H), 3.66 (s, 3H), 2.48 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 157.0 (+), 148.0 (+), 146.7 (+), 144.0 (+), 129.8 (−), 129.2 (−), 127.2 (−), 126.7 (−), 125.8 (−), 123.8 (+), 123.5 (−), 122.3 (−), 112.2 (−), 38.6 (−), 18.9 ppm (−); elemental analysis calcd (%) for $C_{17}H_{16}N_2$: C 82.22, H 6.49, N 11.28; found: C 81.97, H 6.79, N 11.37.

4-(Pyrazin-2-yl)morpholine (35) (Table 5): Following general procedure B, 142 mg of **35** (86 % yield) were isolated (R_f = 0.4, Et_2O) as an off-white solid (m.p. 46–48 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, J = 1.5 Hz, 1H), 8.10–8.04 (m, 1H), 7.91 (d, J = 2.4 Hz, 1H), 3.84 (t, J = 2.4 Hz, 4H), 3.58 ppm (t, J = 2.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ = 155.1 (+), 141.8 (−), 133.6 (−), 130.9 (−), 66.5 (+), 44.8 ppm (+); elemental analysis calcd (%) for $C_8H_{11}N_3O_2$: C 58.17, H 6.71, N 25.44; found: C 58.18, H 6.90, N 25.27.

6-Methoxy-*N*-methyl-*N*-phenyl-2-aminopyridine (36) (Table 5): Following general procedure B, 201 mg of **36** (94 % yield) were isolated (R_f = 0.2, step gradient, pentane followed by 2 % Et_2O in pentane) as an off-white solid (m.p. 44–45 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, J = 8.0 Hz, 2H), 7.35–7.20 (m, 4H), 6.12 (d, J = 4.0 Hz, 1H), 6.10 (d, J = 3.6 Hz, 1H), 3.95 (s, 3H), 3.53 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) APT: δ 163.2 (+), 157.6 (+), 146.8 (+), 139.4 (−), 129.4 (−), 126.3 (−), 125.2 (−), 100.1 (−), 97.3 (−), 53.1 (−), 38.1 ppm (−); elemental analysis

calcd (%) for $C_{13}H_{14}N_2O$: C 72.87, H 6.59, N 13.07; found: C 72.93, H 6.86, N 13.08.

2-(4-Phenylpiperazin-1-yl)pyrazine (37) (Table 5): Following general procedure B, 223 mg of **37** (93% yield) were isolated (R_f = 0.6, 90% Et_2O in pentane) as yellow crystals (m.p. 113–115 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, J = 1.5 Hz, 1H), 8.13–8.06 (m, 1H), 7.91 (d, J = 2.7 Hz, 1H), 7.38–7.27 (m, 2H), 7.05–6.90 (m, 3H), 3.79 (t, J = 5.4 Hz, 4H), 3.34 ppm (t, J = 5.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 155.0 (+), 151.1 (+), 141.8 (−), 133.3 (−), 131.2 (−), 129.3 (−), 120.4 (−), 116.5 (−), 49.1 (+), 44.6 ppm (+); elemental analysis calcd (%) for $C_{14}H_{16}N_4$: C 69.97, H 6.71, N 23.32; found: C 70.27, H 6.58, N 23.15.

Ethyl 1-(pyrazin-2-yl)piperidine-3-carboxylate (38) (Table 5): Following general procedure B, 164 mg of **38** (69% yield) were isolated (R_f = 0.3, Et_2O) as a viscous, yellow oil. The spectral data were in accordance with those reported in the literature.[39]

***N*-Methyl-*N*-phenyl-2-aminopyrazine (39)** (Table 5): Following general procedure B, 165 mg of **39** (89% yield) were isolated (R_f = 0.35, 50% Et_2O in pentane) as a viscous, yellow oil. The spectral data were in accordance with those reported in the literature.[40]

1-Methyl-4-(1-phenyl-1*H*-tetrazol-5-yl)piperazine (40) (Table 5): Following general procedure B, 221 mg of **40** (90% yield) were isolated (R_f = 0.25, 10% ethanol in ethyl acetate) as yellow solid (m.p. 84–87 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.40 (m, 5H), 3.25 (t, J = 4.4 Hz, 4H), 2.43 (t, J = 4.4 Hz, 4H), 2.27 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 157.4 (+), 134.8 (+), 129.8 (−), 129.7 (−), 123.7 (−), 53.9 (+), 48.5 (+), 46.0 ppm (−); elemental analysis calcd (%) for $C_{12}H_{16}N_6$: C 59.00, H 6.60, N 34.40; found: C 58.71, H 6.97, N 33.99.

(*S*)-*N*-(1-(Naphthalene-1-yl)ethyl)isoquinolin-3-amine (41) (Table 5): Following general procedure B, 286 mg of **41** (96% yield) were isolated (R_f = 0.4, 20% Et_2O in pentane) as a pale yellow solid (m.p. 53–56 °C). $[\alpha]_D^{20}$ = +28.1° (c = 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27–8.15 (m, 1H), 8.06 (d, J = 6.0 Hz, 1H), 7.9–7.78 (m, 2H), 7.70–7.62 (m, 3H), 7.60–7.52 (m, 1H), 7.50–7.45 (m, 3H), 7.42–7.35 (m, 1H), 6.96 (d, J = 5.7 Hz, 1H), 6.35 (quin., J = 6.6 Hz, 1H), 5.45 (br. d, J = 6.9 Hz, 1H) 1.84 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 153.2 (+), 141.7 (−), 139.7 (+), 137.2 (+), 134.0 (+), 131.5 (+), 129.6 (−), 128.7 (−), 128.1 (−), 127.2 (−), 126.3 (−), 125.8 (−), 125.7 (−), 125.4 (−), 123.9 (−), 122.6 (−), 121.4 (−), 118.0 (+), 110.9 (−), 46.3 (−), 20.7 ppm (−); elemental analysis calcd (%) for $C_{20}H_{18}N_2$: C 84.53, H 6.08, N 9.39; found: C 84.56; H 6.00, N 9.22.

***N*,*N*-Bis(2-methoxyethyl)-2-aminopyrazine (42)** (Table 5): Following general procedure B, 203 mg of **42** (96% yield) were isolated (R_f = 0.45, step gradient, 10% Et_2O in pentane followed by 25% Et_2O in pentane) as a viscous, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 2.7, 1.7 Hz, 1H), 7.72 (d, J = 2.7 Hz, 1H), 3.71 (t, J = 5.7 Hz, 4H), 3.54 (t, J = 5.7 Hz, 4H), 3.31 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 153.9 (+), 141.5 (−), 131.5 (−), 130.3 (−), 70.4 (+), 58.9 (−), 48.7 ppm (+); elemental analysis calcd (%) for $C_{10}H_{17}N_3O_2$: C 56.85, H 8.11, N 19.89; found: C 56.85; H 8.21, N 19.92.

6-Methoxy-*N*,*N*-bis(2-methoxyethyl)pyridin-2-amine (43) (Table 5): Following general procedure B, 149 mg of **43** (62% yield) were isolated (R_f = 0.25, step gradient, 5% Et_2O in pentane followed by 20% Et_2O in pentane) as a viscous, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (t, J = 6.0 Hz, 1H), 6.09 (d, J = 6.0 Hz, 1H), 6.00 (d, J = 6.0 Hz, 1H), 3.86 (s, 3H), 3.72 (t, J = 4.6 Hz, 4H), 3.60 (t, J = 4.6 Hz, 4H), 3.38 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 163.0 (+), 156.7 (+), 139.8 (−), 96.8 (−), 96.2 (−), 70.7 (+), 58.9 (−), 52.7 (−), 49.2 ppm (+); elemental analysis calcd (%) for $C_{12}H_{20}N_2O_3$: C 59.98, H 8.39, N 11.66; found: C 60.39; H 8.11, N 11.99.

***N*,*N*-Diphenylpyrazin-2-amine (44)** (Table 5): Following general procedure B, 205 mg of **44** (83% yield) were isolated (R_f = 0.25, step gradient, 15% Et_2O in pentane followed by 25% Et_2O in pentane) as a pale yellow solid (m.p. 70–73 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15–8.08 (m, 2H), 7.99 (d, J = 2.7 Hz, 1H), 7.40–7.33 (m, 4H), 7.25–7.17 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 155.2 (+), 144.7 (+), 141.9 (−), 136.2 (−), 135.5 (−), 129.8 (−), 126.5 (−), 125.7 ppm (−); elemental analysis calcd (%) for $C_{16}H_{13}N_3$: C 77.71, H 5.30, N 16.99; found: C 77.40; H 5.44, N 16.66.

***N*-Allyl-*N*-phenylpyrazin-2-amine (45)** (Table 5): Following general procedure B, 201 mg of **45** (95% yield) were isolated (R_f = 0.2, 20% Et_2O in pentane) as a yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.83 (d, J = 2.7 Hz, 1H), 7.48–7.39 (m, 2H), 7.31–7.25 (m, 3H), 6.05–5.96 (m, 1H), 5.23–5.12 (m, 2H), 4.55 ppm (dt, J = 5.4, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 154.2 (+), 143.9 (+), 141.5 (−), 133.6 (−), 133.0 (−), 132.9 (−), 130.0 (−), 127.0 (−), 126.7 (−), 116.9 (+), 52.7 ppm (+); elemental analysis calcd (%) for $C_{13}H_{13}N_3$: C 73.91, H 6.20, N 19.89; found: C 74.20; H 6.52, N 19.89.

***N*-Methyl-*N*,6-diphenyl-3-aminopyridazine (46)** (Table 5): Following general procedure B, 204 mg of **46** (78% yield) were isolated (R_f = 0.4, 40 vol% Et_2O in pentane) as an off-white solid (m.p. 112–114 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.5 Hz, 2H), 7.50–7.30 (m, 6H), 7.30–7.20 (m, 3H), 6.80 (d, J = 9.3 Hz, 1H), 3.66 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) APT: δ 158.4 (+), 151.2 (+), 145.5 (+), 136.8 (+), 130.1 (−), 128.8 (−), 128.7 (−), 126.5 (−), 125.9 (−), 124.4 (−), 114.8 (−), 38.9 ppm (−); overlapping peaks in the aromatic region account for the remaining ^{13}C resonances; elemental analysis calcd (%) for $C_{17}H_{15}N_3$: C 78.13, H 5.79, N 16.08; found: 77.80, H 6.06, N 15.87.

6-Methoxy-*N*-methyl-*N*-phenyl-3-aminopyridazine (47) (Table 5): Following general procedure B, 112 mg of **47** (52% yield) were isolated (R_f = 0.4, 40% Et_2O in pentane) as a off-white solid (m.p. 76–77 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, J = 8.0 Hz, 2H), 7.25–7.15 (m, 3H), 6.82 (d, J = 10.0 Hz, 1H), 6.66 (d, J = 9.6 Hz, 1H), 4.03 (s, 3H), 3.52 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) APT: δ 160.0 (+), 156.7 (+), 146.5 (+), 129.9 (−), 125.8 (−), 125.7 (−), 120.3 (−), 118.7 (−), 54.3 (−), 39.1 ppm (−); elemental analysis calcd (%) for $C_{12}H_{15}N_3O$: C 66.96, H 6.09, N 19.52; found: 67.19, H 6.33, N 19.42.

5-(Morpholino-4-yl)pyrimidine (48) (Table 6): Following general procedure C, 138 mg of **48** (84% yield) were isolated (R_f = 0.30, ethyl acetate) as a pale yellow oil. The spectral data were in accordance with those reported in the literature.[41]

5-(Piperidin-1-yl)pyrimidine (49) (Table 6): Following general procedure C, 117 mg of **49** (72% yield) were isolated (R_f = 0.4, ethyl acetate) as a yellow oil. The spectral data were in accordance with those reported in the literature.[42]

***N*-Benzyl-*N*-methylpyrimidin-5-amine (50)** (Table 6): Following general procedure C, 130 mg of **50** (65% yield) were isolated (R_f = 0.30, 50 vol% ethyl acetate in pentane) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.21 (s, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.27 (d, J = 7.1 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 4.55 (s, 2H), 3.09 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1, 142.5, 139.9, 136.8, 128.7, 127.3, 126.4, 55.3, 37.9 ppm; elemental analysis calcd (%) for $C_{12}H_{13}N_3$: C 72.33, H 6.58, N 21.09; found: C 71.95, H 6.81, N 20.93.

5-(4-Ethylpiperazin-1-yl)pyrimidine (51) (Table 6): Following general procedure C, 153 mg of **51** (80% yield) were isolated (R_f = 0.25, 10% methanol in ethyl acetate) as a colorless oil. The spectral data were in accordance with those reported in the literature.[42]

***N*-Methyl-*N*-phenyl-3-aminopyridine (52)** (Table 6): Following general procedure C, 103 mg of **52** (56% yield) were isolated (R_f = 0.25, 10% ethyl acetate in pentane) as a pale yellow oil. The spectral data were in accordance with those reported in the literature.[43]

***N*-Benzyl-*N*-methylpyridin-3-amine (53)** (Table 6): Following general procedure C, 110 mg of **53** (56% yield) were isolated (R_f = 0.35, 30% ethyl acetate in pentane) as a yellow oil. The spectral data were in accordance with those reported in the literature.[44]

***N*-Methyl-*N*-phenylpyrimidin-5-amine (54)** Table 6): Following general procedure C, 148 mg of **55** (80% yield) were isolated (R_f = 0.25, 50% ethyl acetate in pentane) as a yellow oil. The spectral data were in accordance with those reported in the literature.[41]

4-(Pyridin-3-yl)morpholine (**55**, Table 6): Following general procedure C, 147 mg of **56** (90% yield) were isolated (R_f = 0.30, ethyl acetate) as a light yellow oil. The spectral data were in accordance with those reported in the literature.[43]

4-*p*-Tolylmorpholine (Figure 3): Following general procedure B, 19 mg (11% yield, X=Br) and 17 mg (10% yield, X=Cl) of title compound were isolated (R_f=0.6, 10% Et_2O in pentane) as white solid (m.p. 44–47°C; lit m.p. 45–48°C). The spectral data were in accordance with those reported in the literature.[45]

4-(4-Nitrophenyl)morpholine (Figure 3): Following general procedure B, 200 mg (96% yield, X=Cl) and 204 mg (98% yield, X=Br) of the title compound were isolated (R_f=0.30, 50% Et_2O in pentane) as a yellow/orange solid (m.p. 145–146°C; lit. m.p. 158–159°C).[46] The spectral data were in accordance with those reported in the literature.[47]

4-(4-Fluorophenyl)morpholine (Figure 3): Following general procedure B, 116 mg (64% yield, X=Cl) and 121 mg (67% yield, X=Br) of the title compound were isolated (R_f=0.30, 20% Et_2O in pentane) as a light yellow oil. The spectral data were in accordance with those reported in the literature.[48]

Acknowledgements

We thank ORDCF and NSERC Canada for financial support, Sigma-Aldrich Inc. for their generous supply of Pd–PEPPSI-IPr for these studies, and Varian Canada for their collaborative in-kind donation (in part) of the GS/MS/MS 4000.

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Received: October 13, 2007
Published online: January 25, 2008

